Division of Case Management:

Overview, Enforcement Activities and the FDA Export Reform and Modernization Act

CBER 101, March 26, 2003

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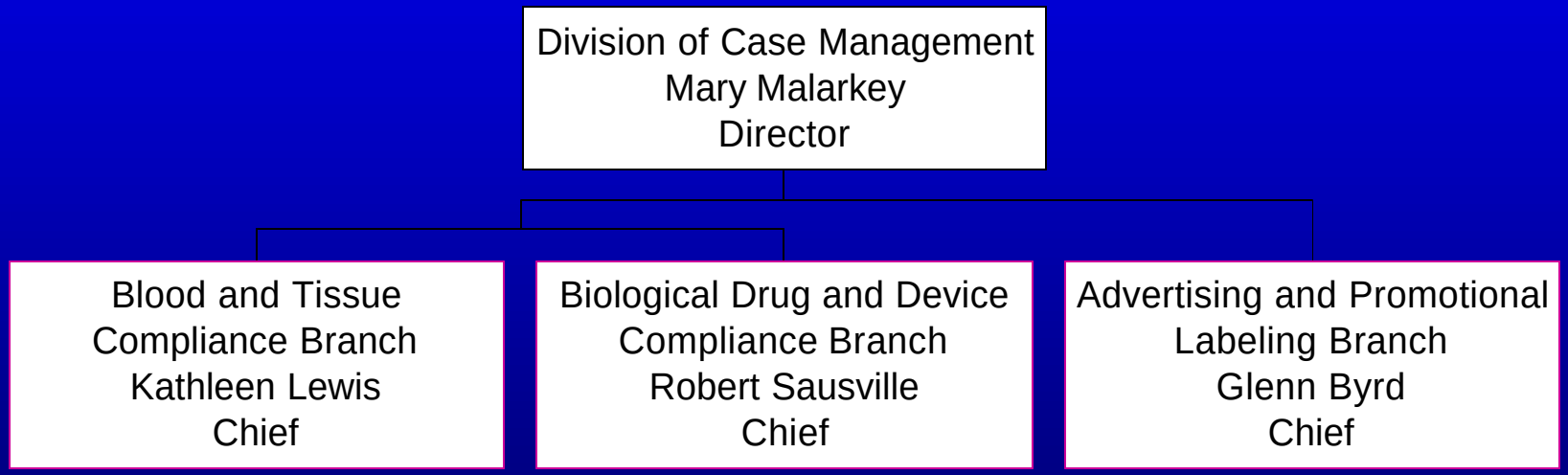
Chief, Biological Drug and Device Compliance Branch
Division of Case Management,
Office of Compliance and Biologics Quality

- Organization
- Functions and data
- Enforcement actions and data

Organization

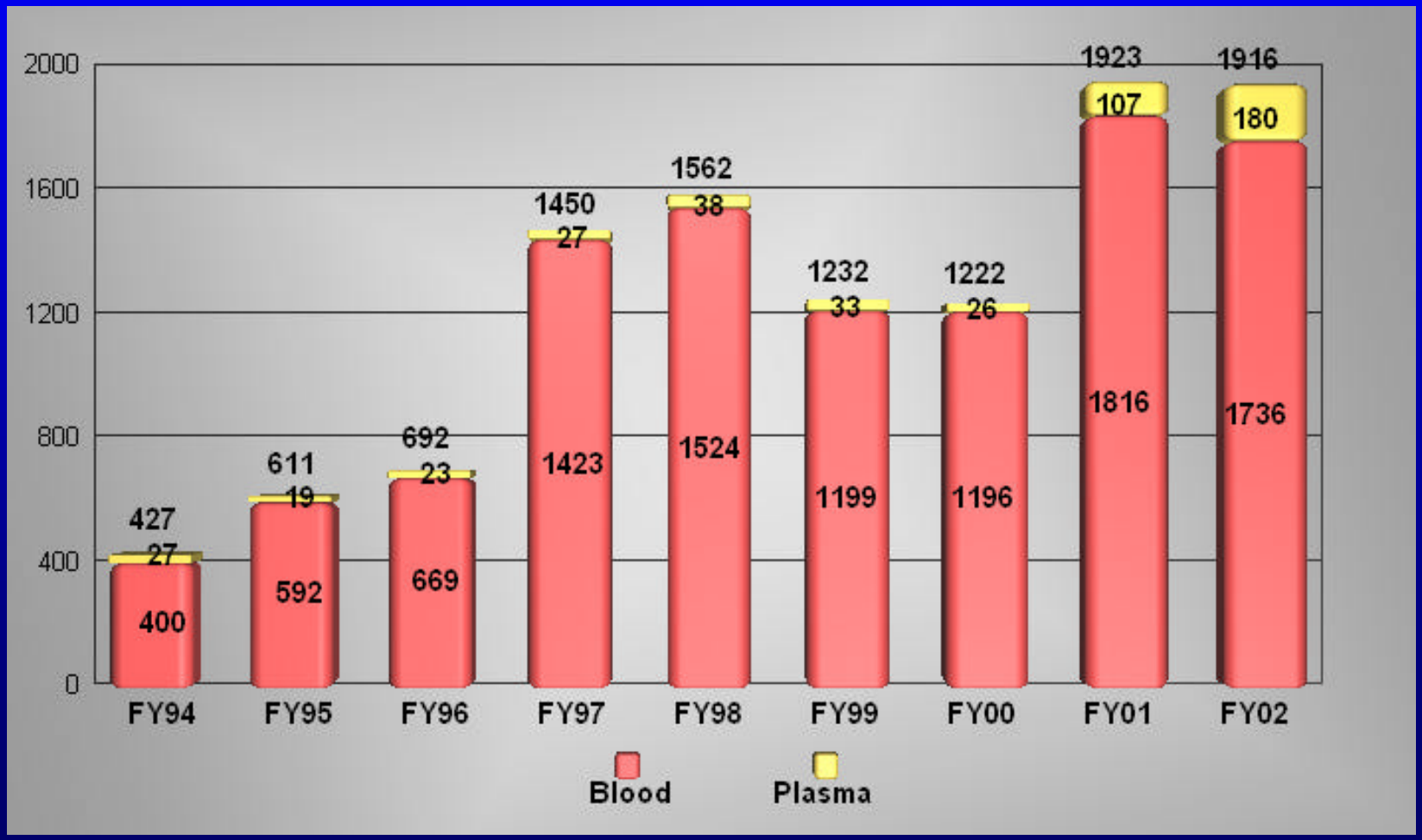


BTCB

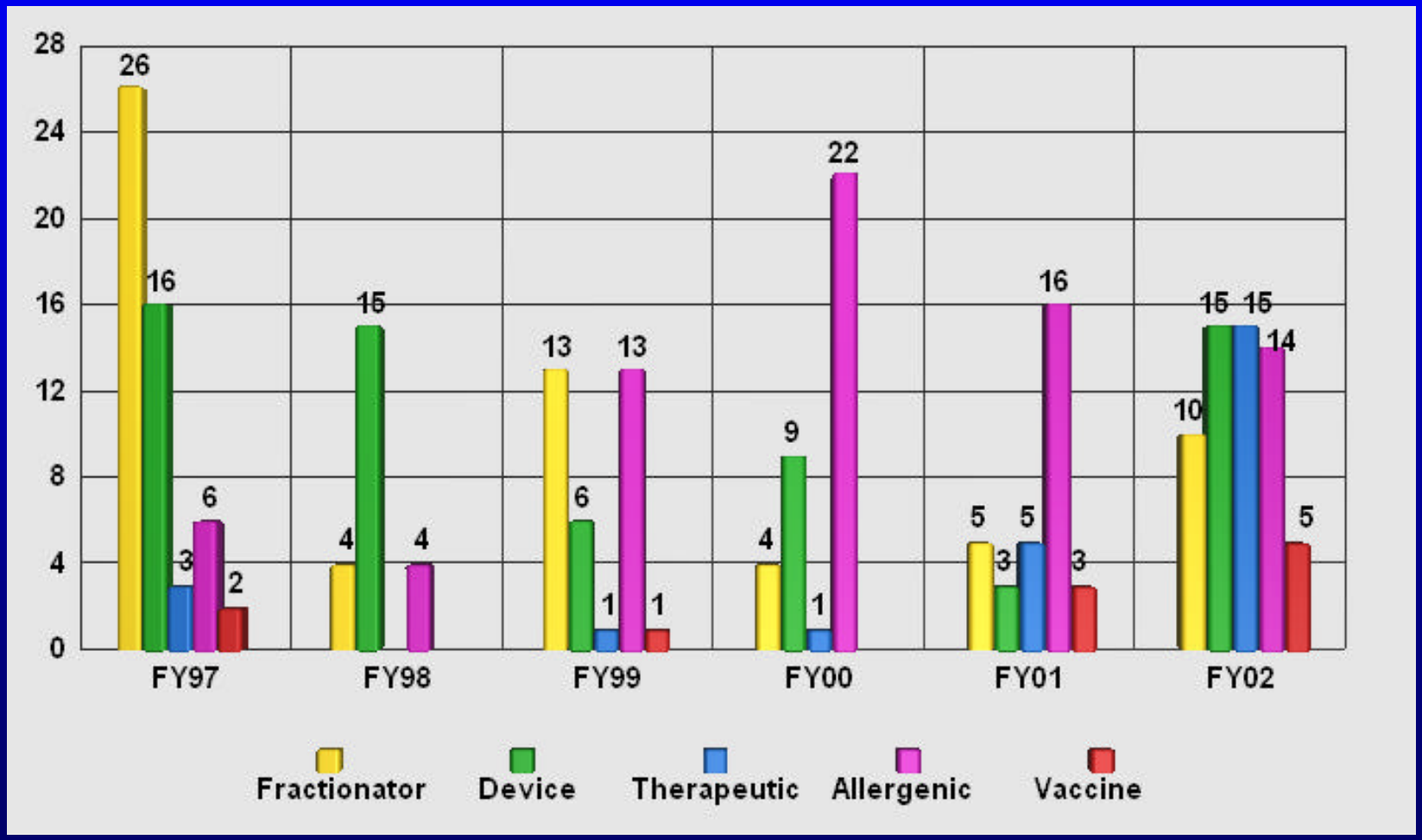
- Blood and plasma enforcement actions and follow-up (administrative and legal) as defined in Regulatory Procedures Manual
- Tissue enforcement actions and follow-up (administrative and legal)
- Recalls - final determination, HHEs

Recalls

Blood and Plasma



Recalls Classified



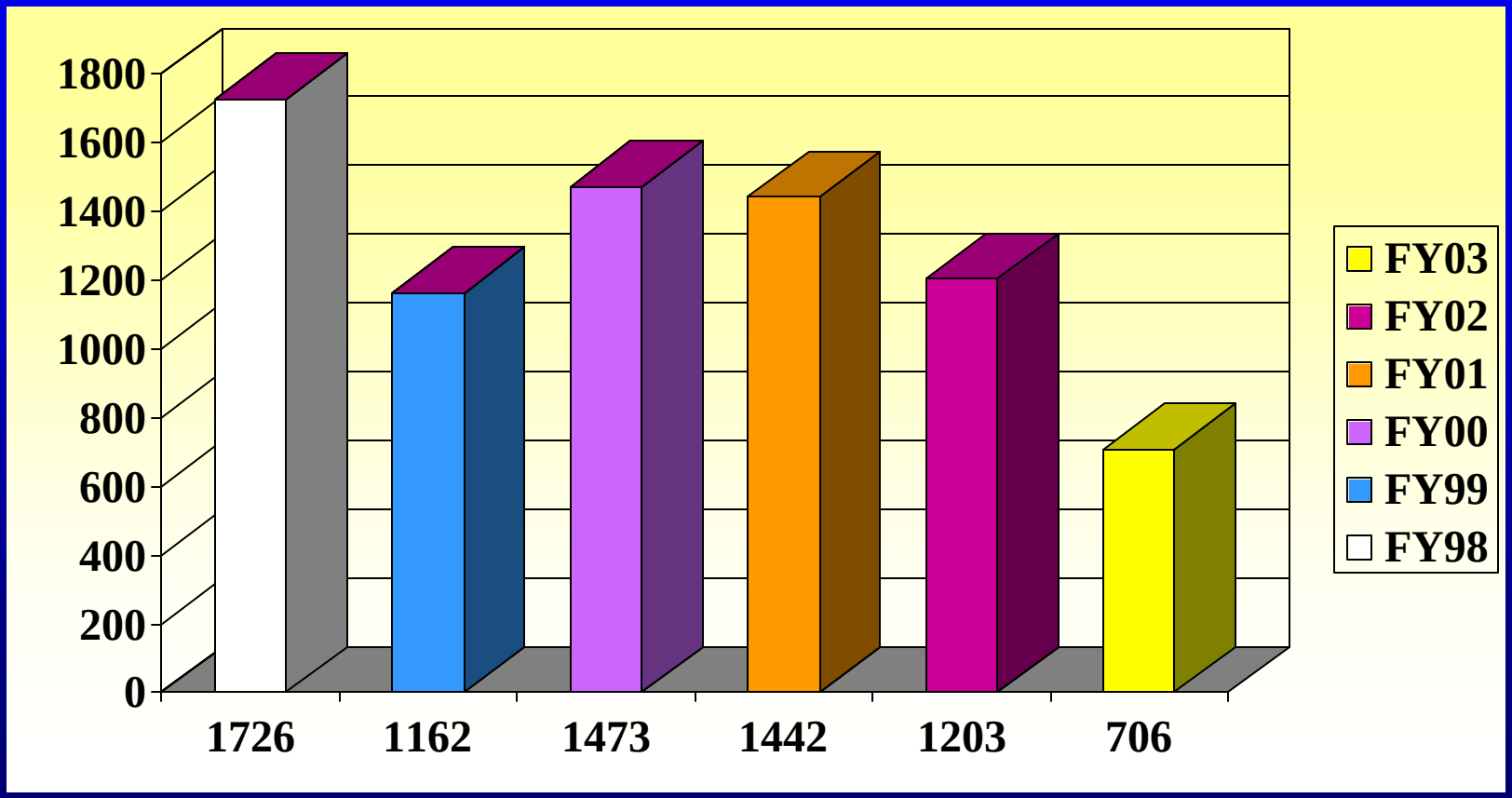
BDDCB

- Core Team Biologics enforcement actions and follow-up (administrative and legal)
- Other drug and device compliance actions e.g. unapproved products and PAIs
- Export/import issues
- Export Certificates
- Compliance Checks

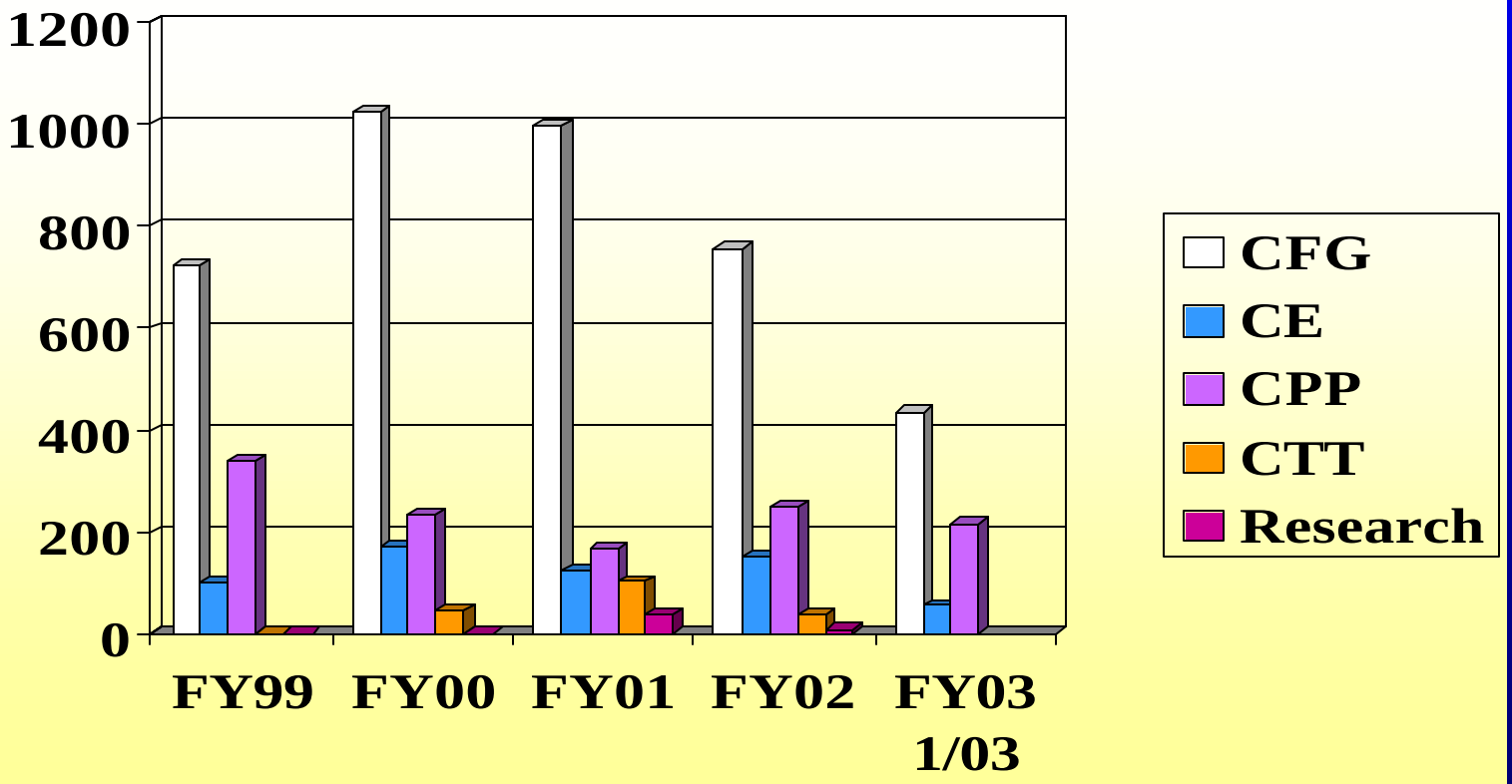
Export Certificates: Types

- Certificates to Foreign Government
  - Export of product legally marketed in US
- Certificates of Exportability
  - Export of product not legally marketed in US
- Certificates of Pharmaceutical Product
  - WHO format -

Export Certificate Totals



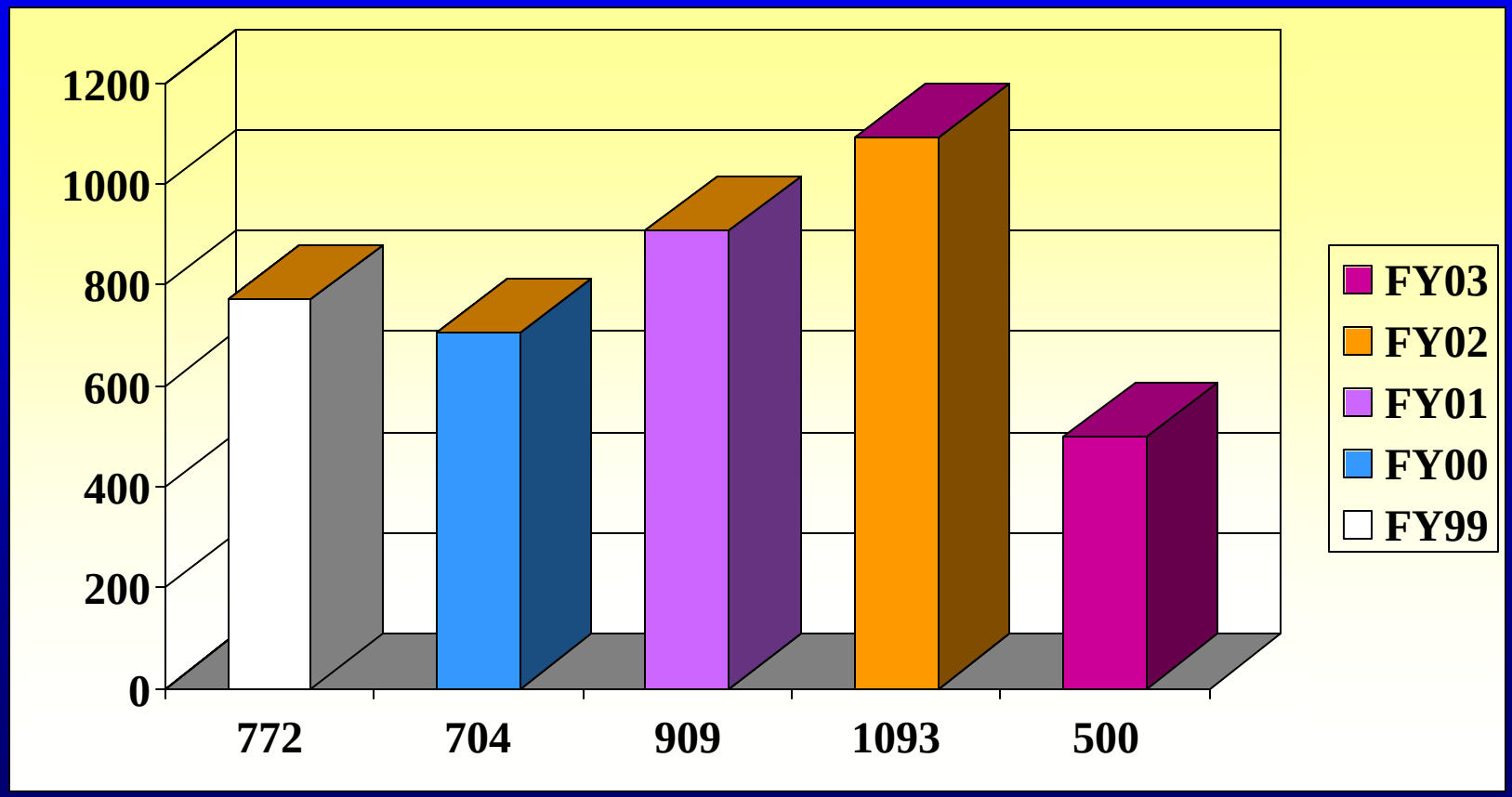
Export Certificates



Compliance Checks

- Performed prior to approval of biologics license applications and major supplements.
- Determination of compliance status of:
  - license holder or potential license holder
  - all manufacturing locations.

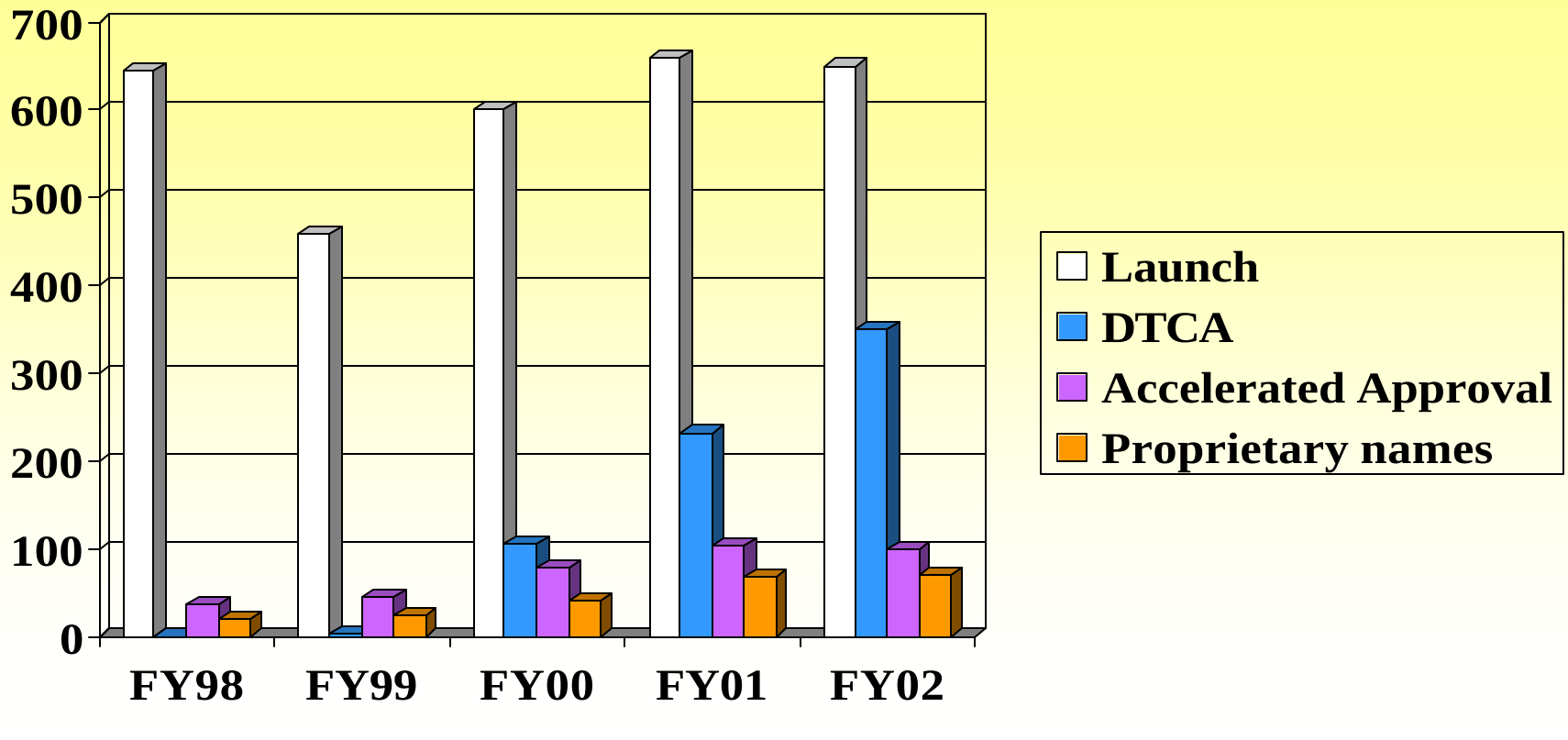
Compliance Checks



APLB

- Review of advertising and promotional labeling (APL) for approved products and those pending approval
- Internet review (with BDDCB)
- Review of proprietary names for products pending approval
- Review of proposed blood donor incentive programs
- Enforcement actions related to APL
- Review of industry complaints

APLB Submissions



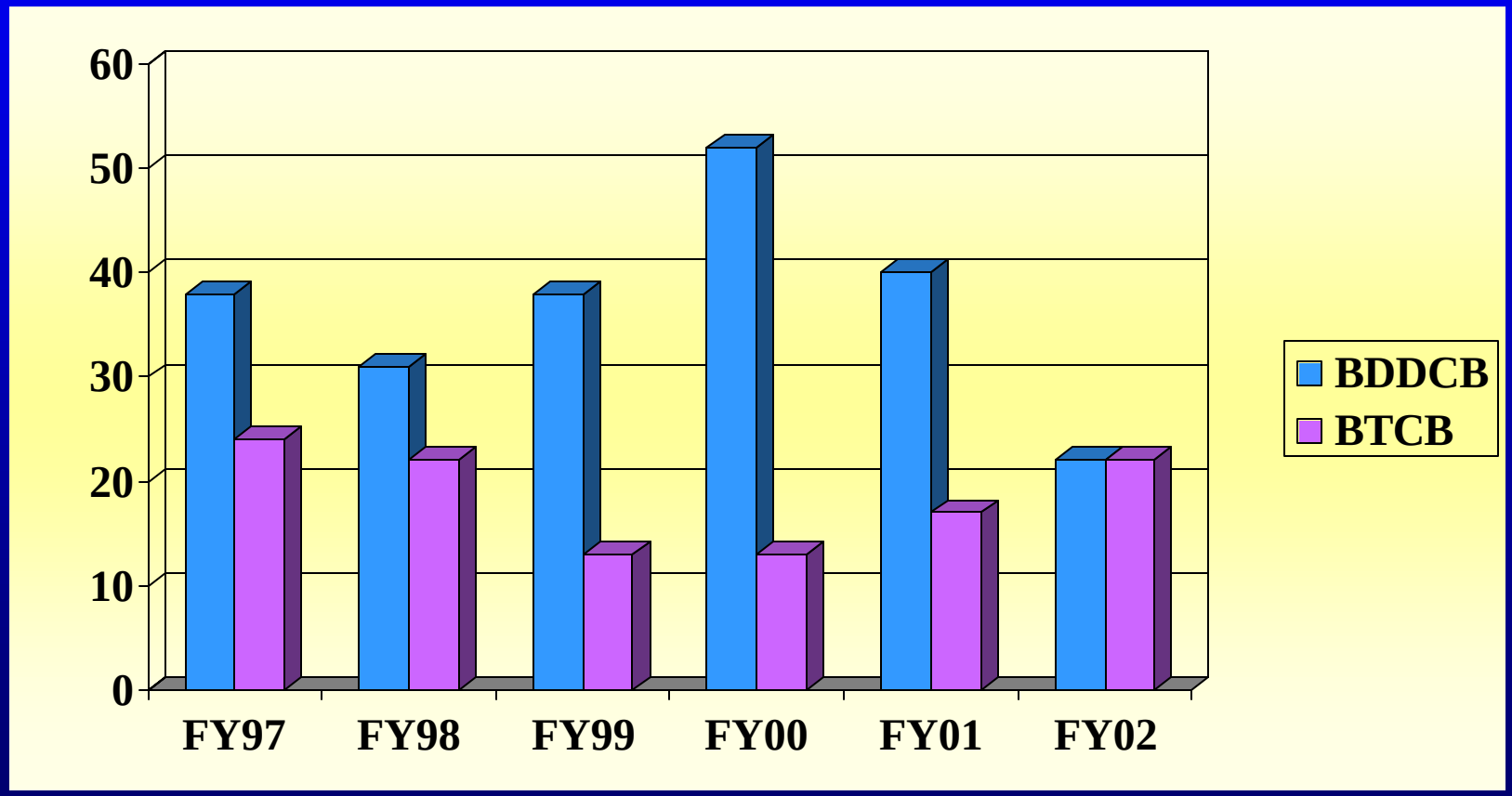
DCM Actions

- Warning Letters
- Seizures
- Injunctions
- Notice of Violation – Adv. and promotion
- License Suspension
- License Revocation
  - Notice of Intent to Revoke
- Other – meeting with firm; untitled letter

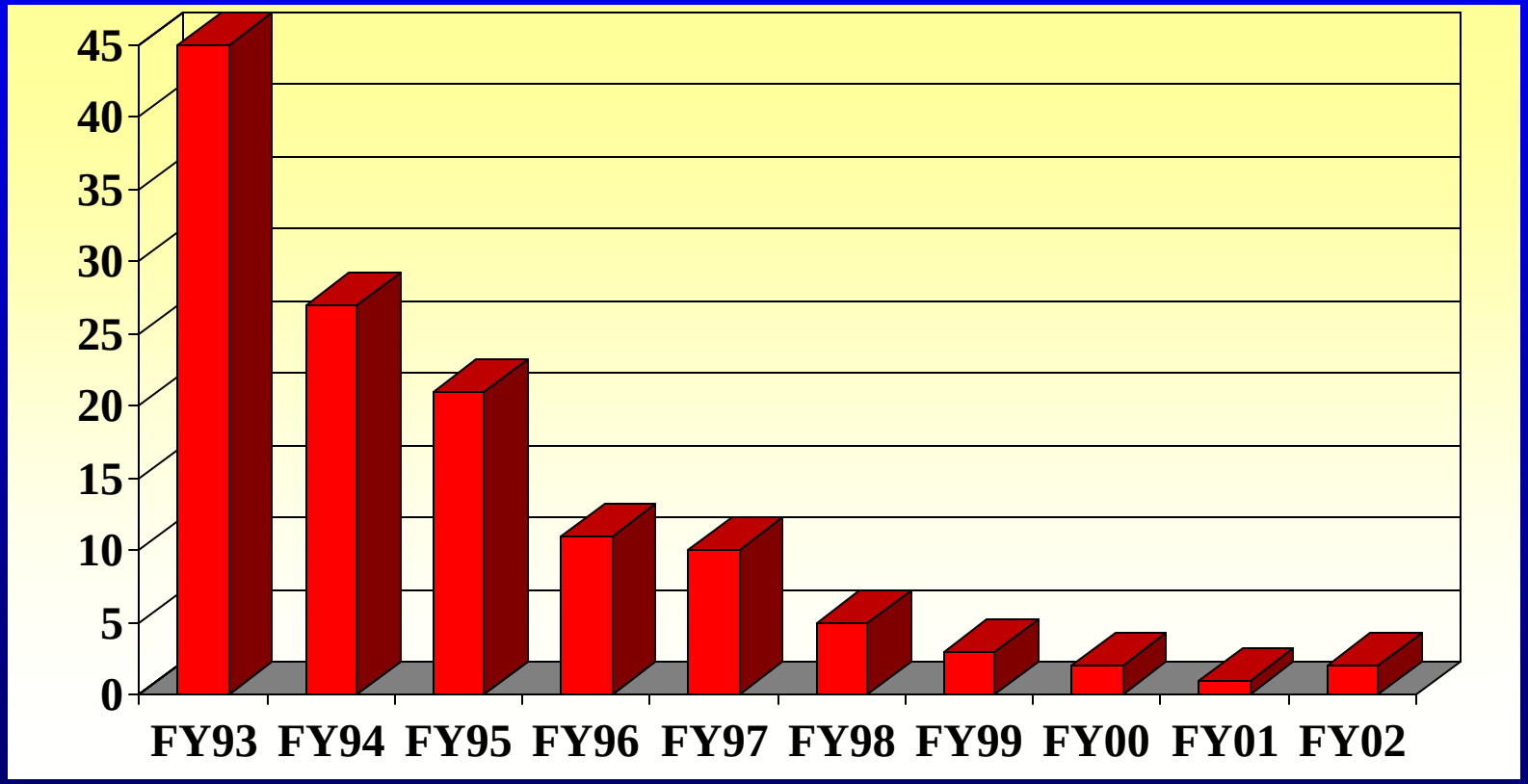
DCM Enforcement Activities

- Blood, Plasma and Tissue
- Team Biologics - Core Team
- Recommendations from FDA district offices
- Unapproved products on internet
- Advertising and Promotional Labeling
  - False and misleading claims

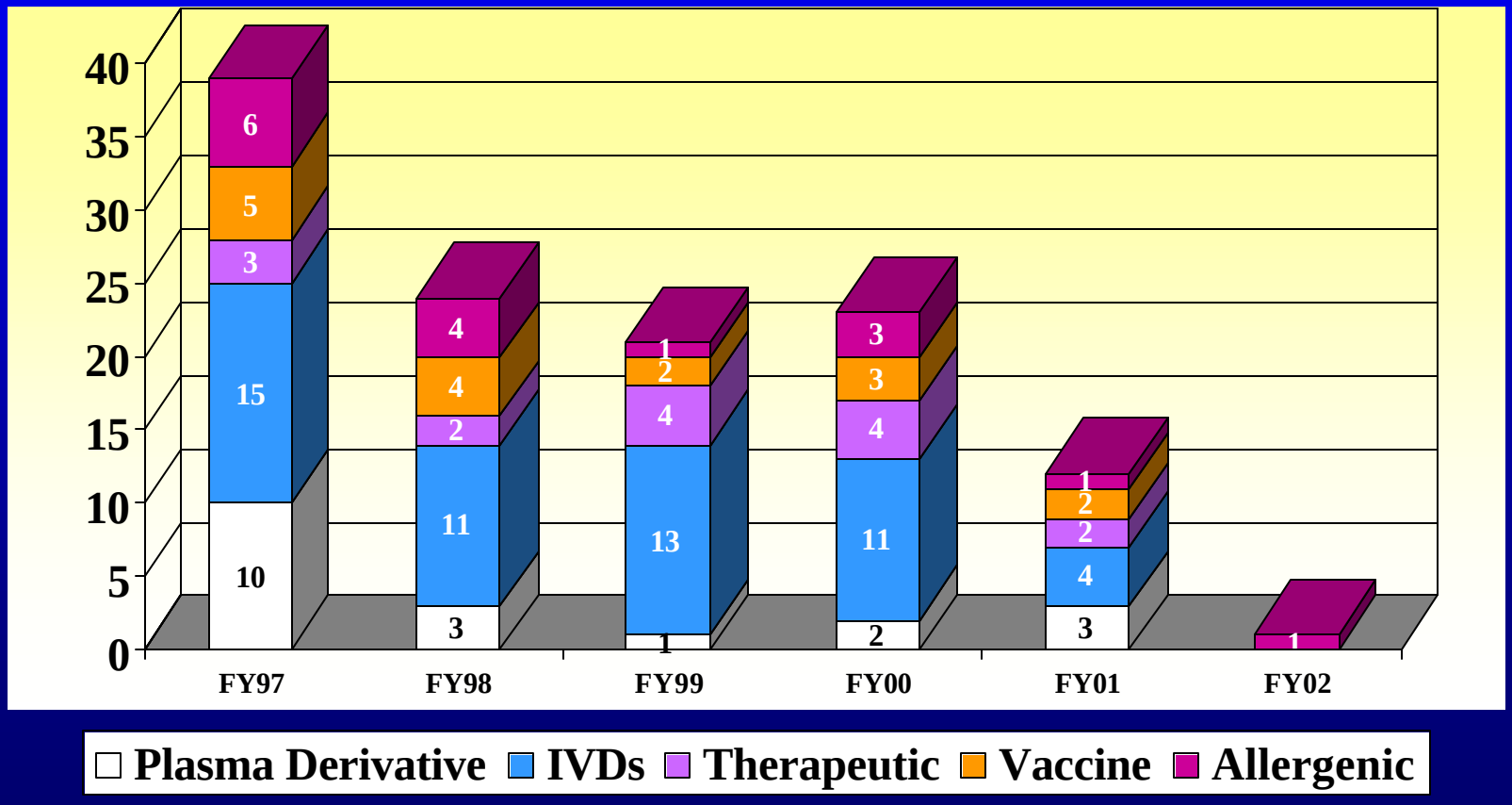
RHS



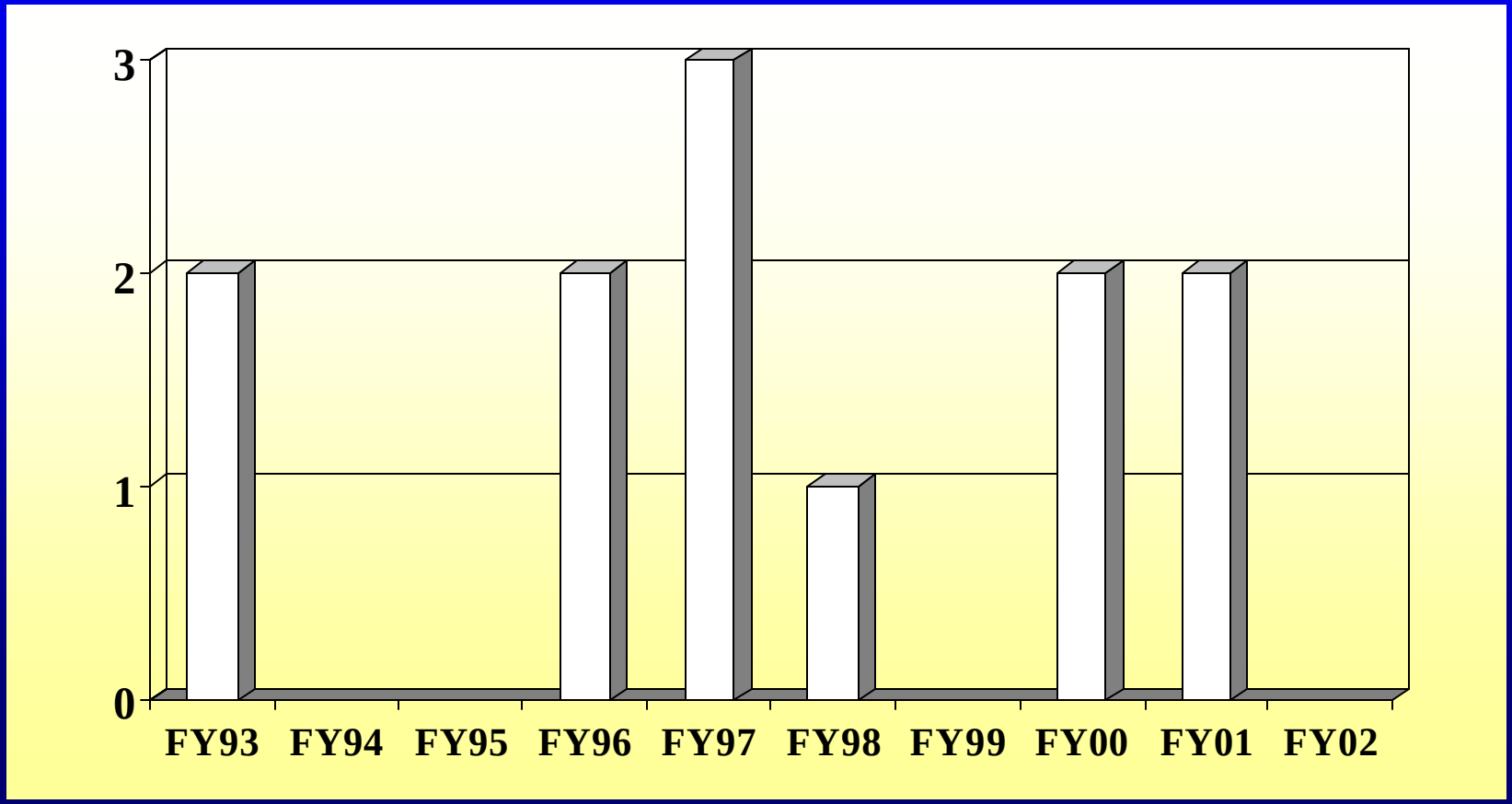
Warning Letters: Blood and Source Plasma



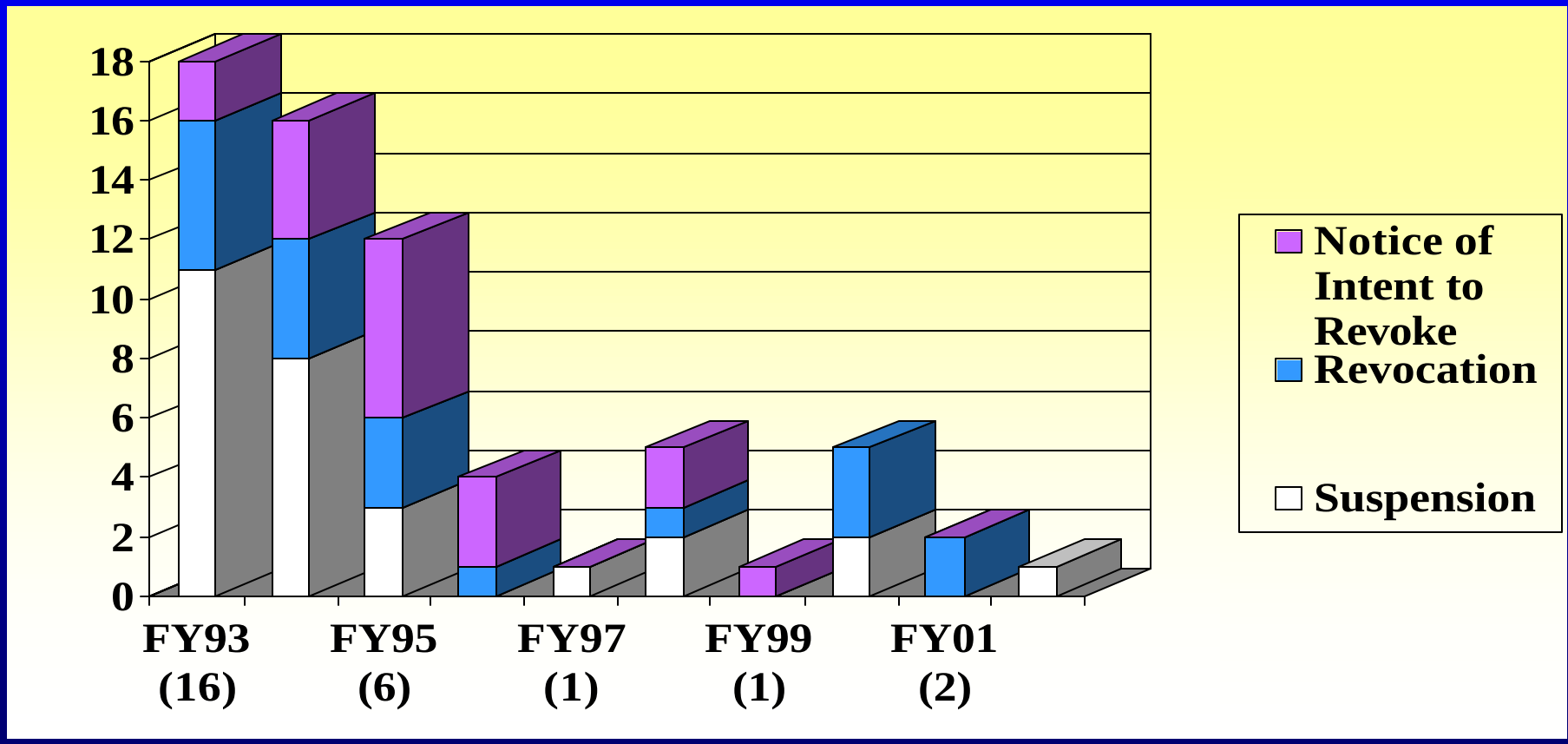
Warning Letters: Biological Drugs and Devices



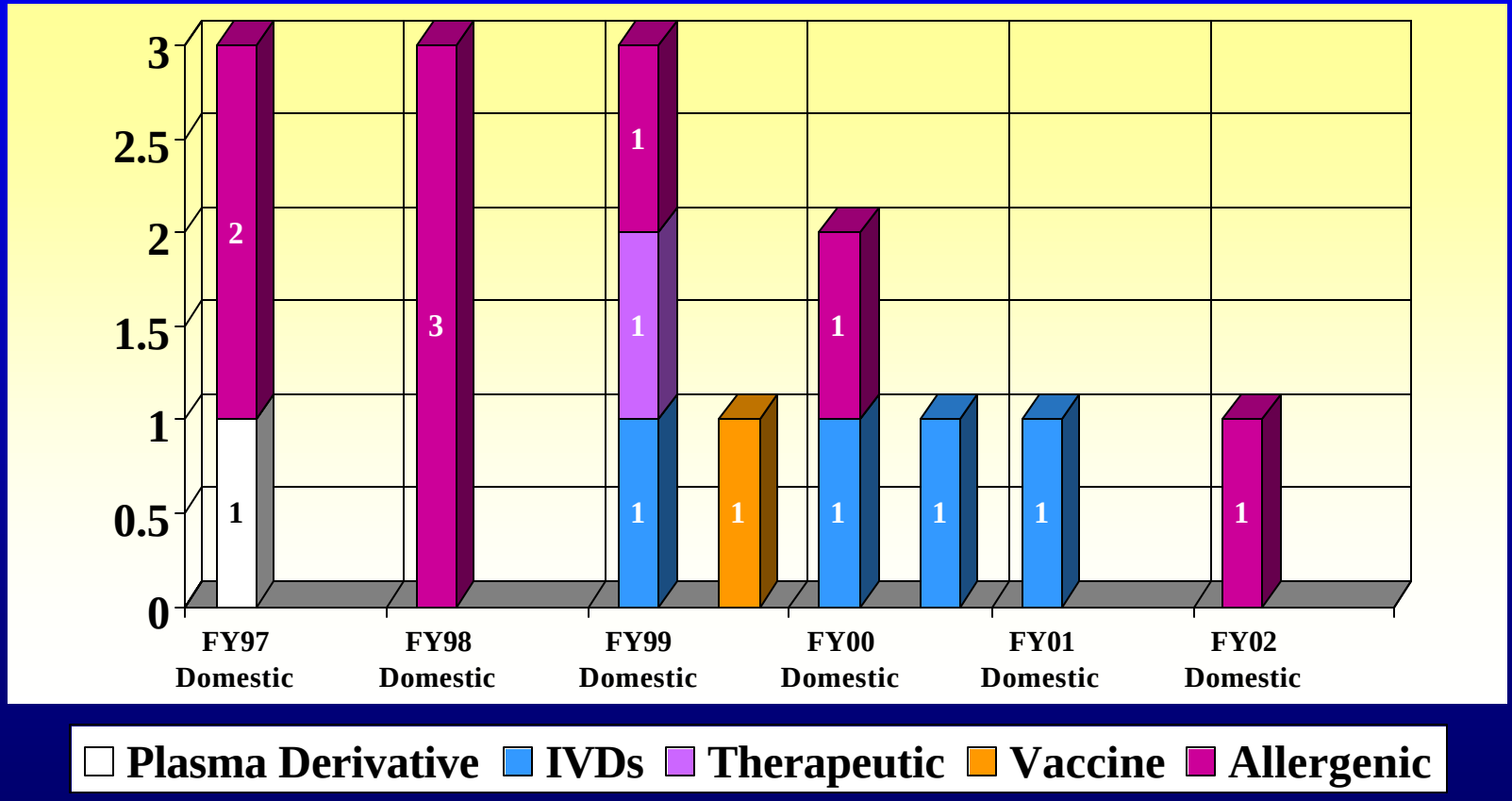
Injunctions



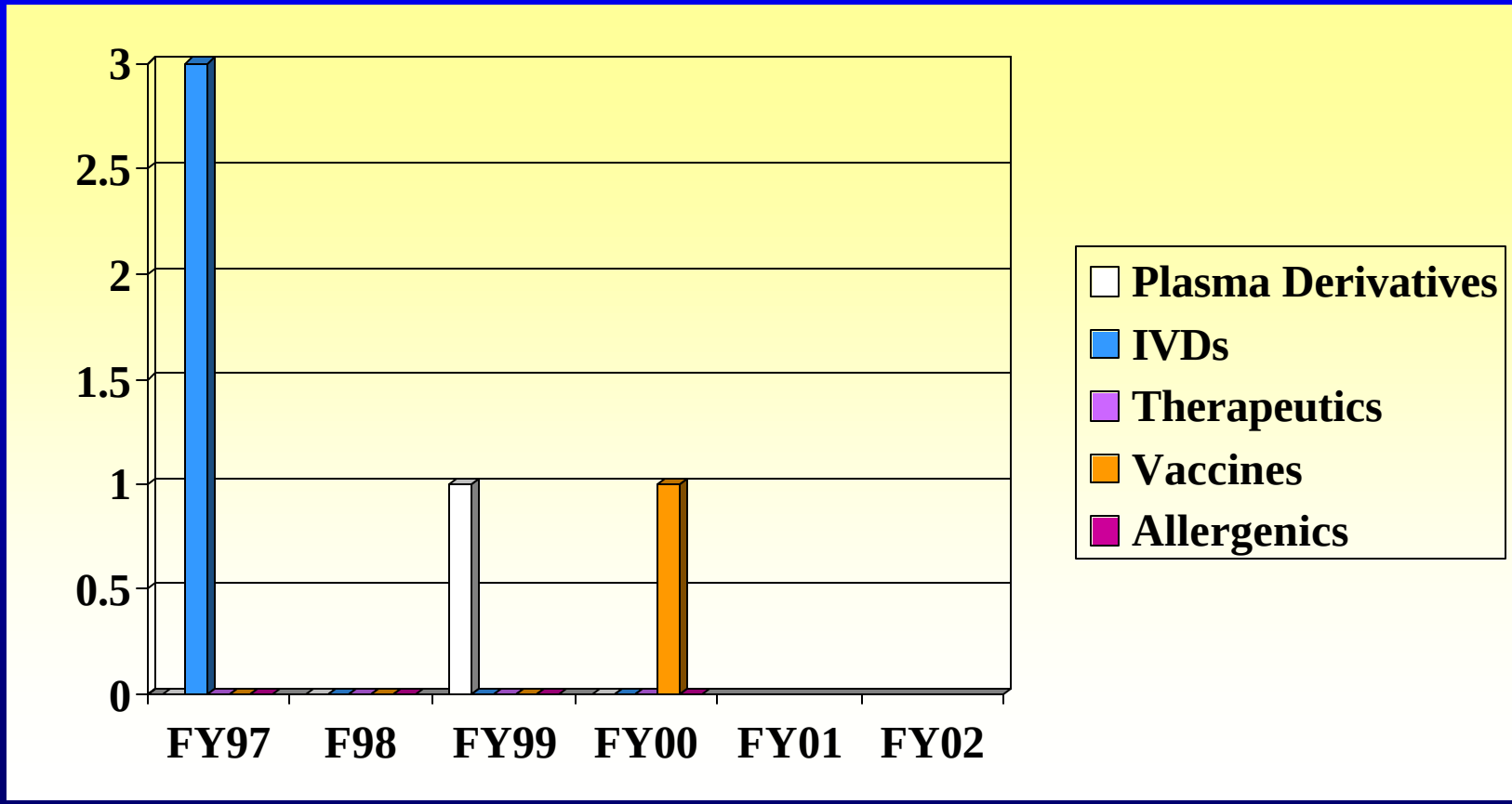
Administrative Actions: Blood and Source Plasma



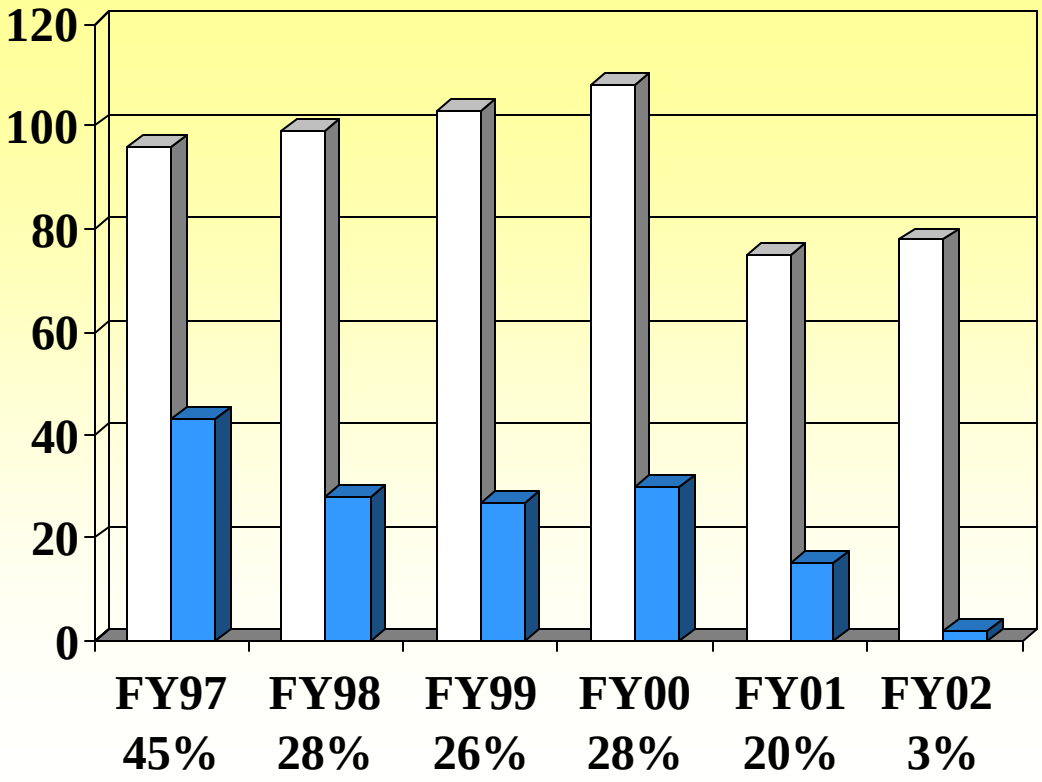
Administrative Actions: Biological Drugs and Devices



Seizures

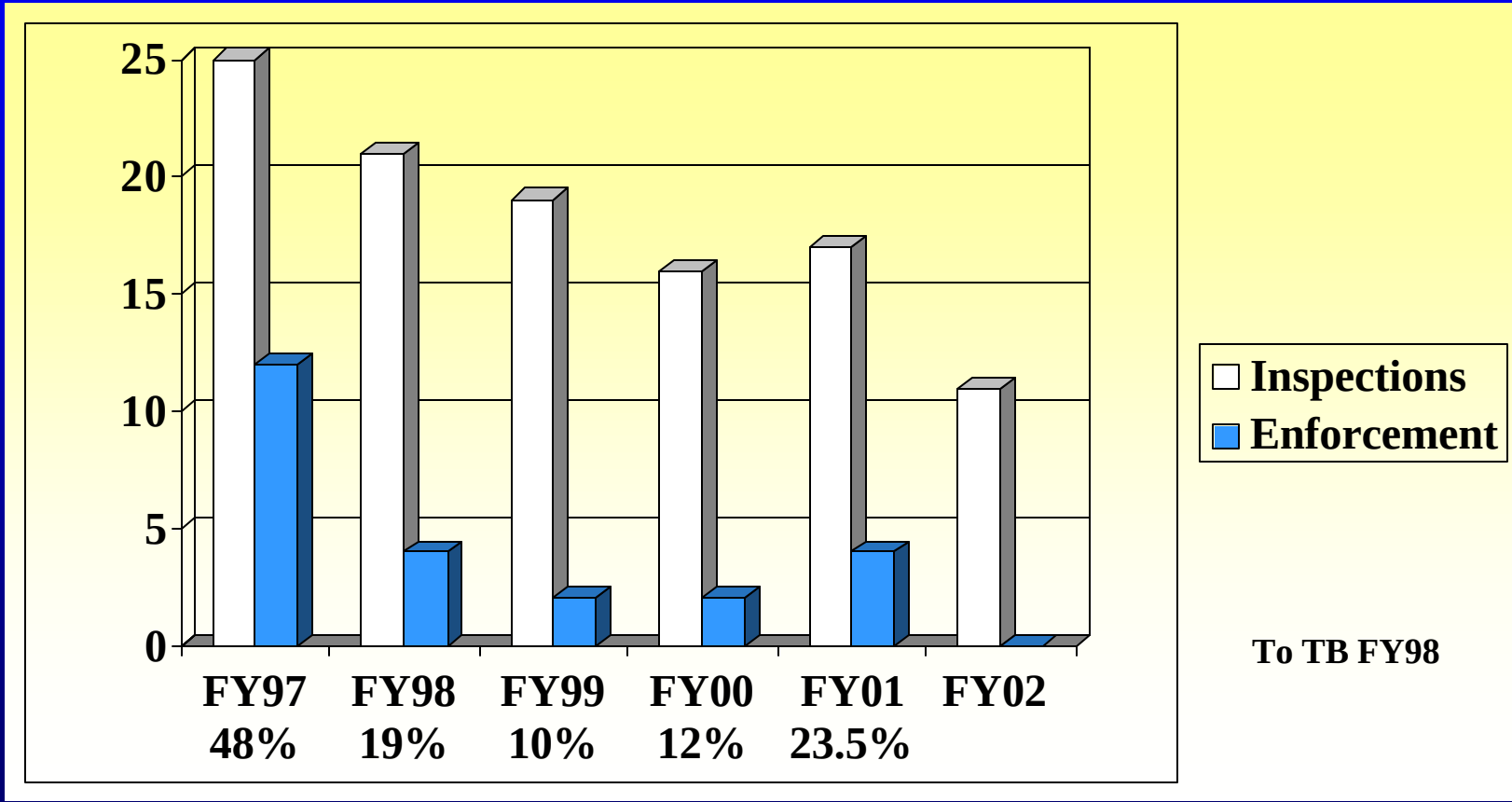

3
2.5
2
1.5
1
0.5
0
FY97
F98
FY99
FY00
FY01
FY02
Plasma Derivatives
IVDs
Therapeutics
Vaccines
Allergenics

Inspections vs. Enforcement

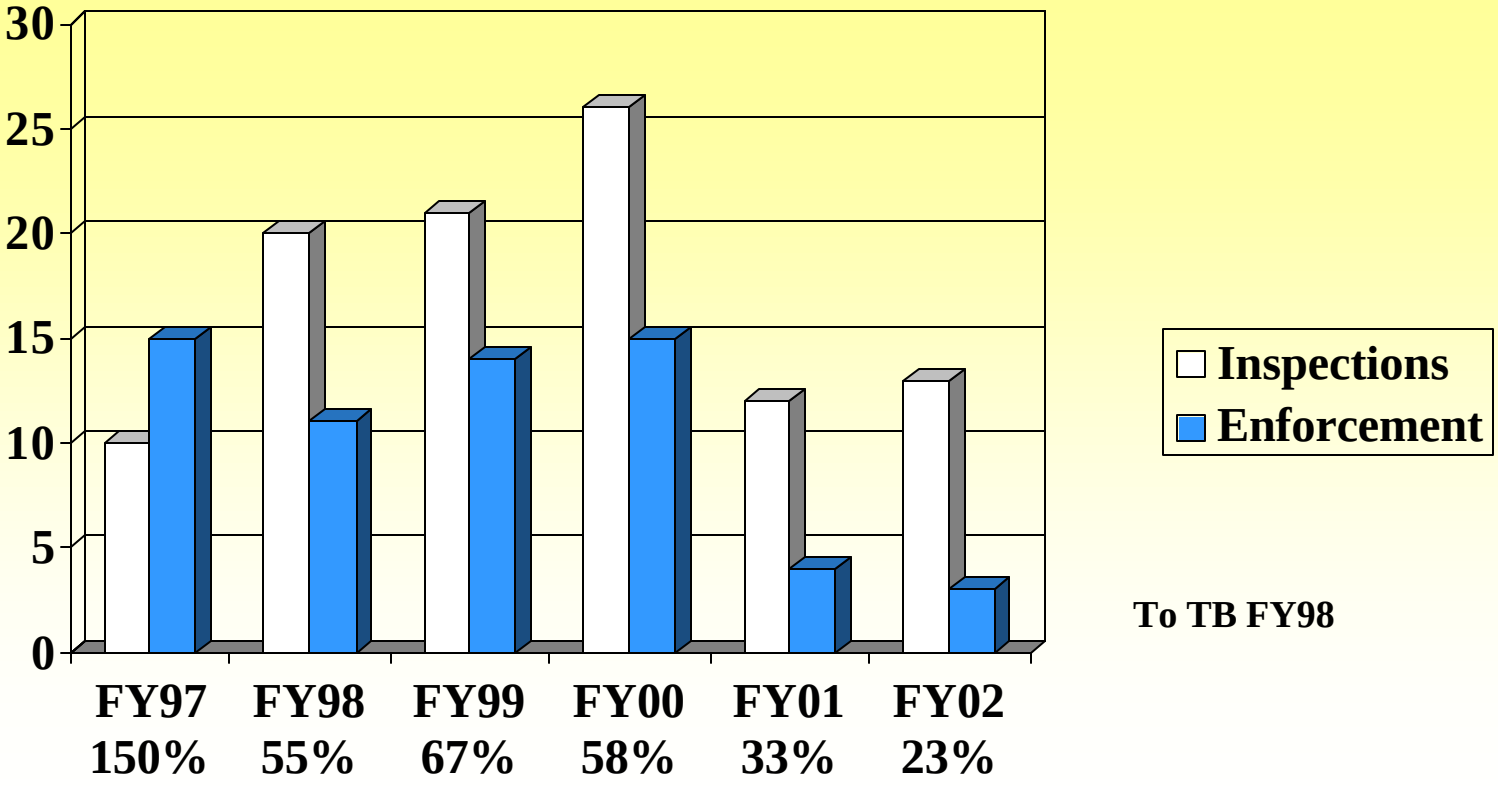


To TB FY99

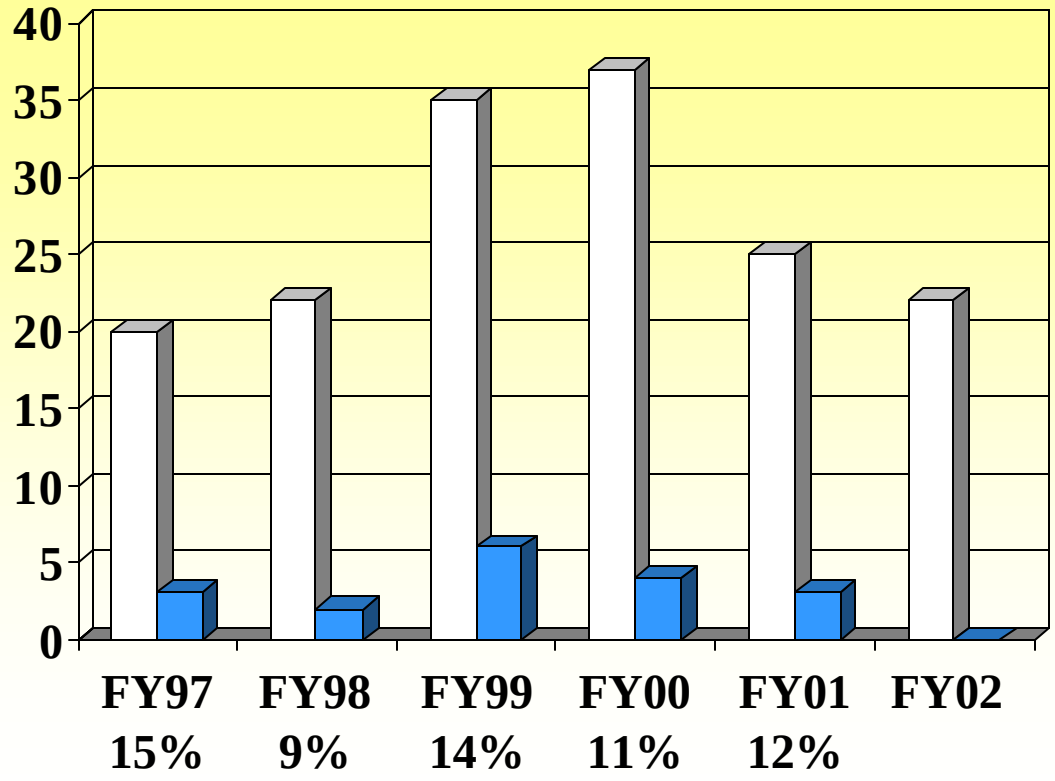
Inspections vs. Enforcement Plasma Derivatives



Inspections vs. Enforcement IVDs

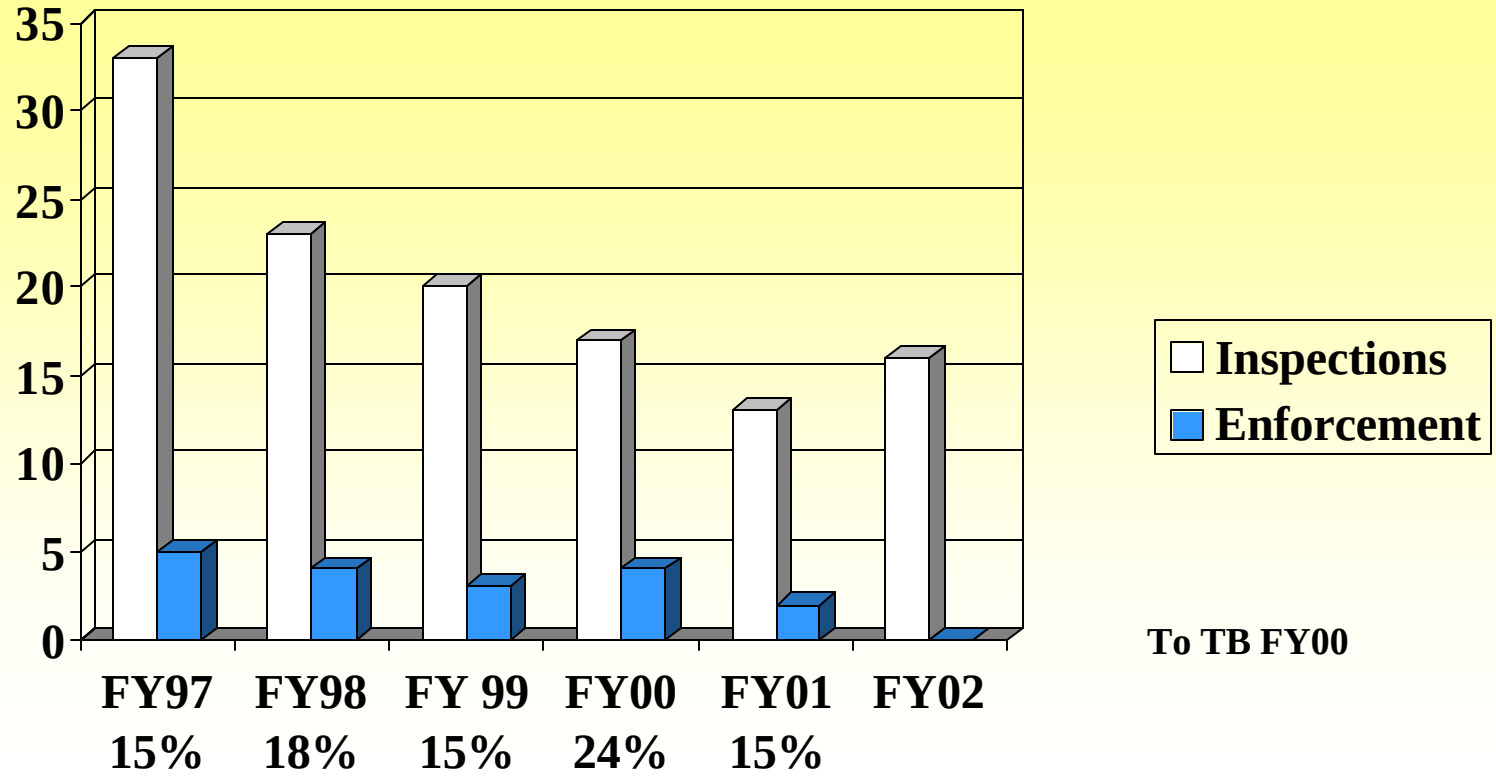


Inspections vs. Enforcement Therapeutics

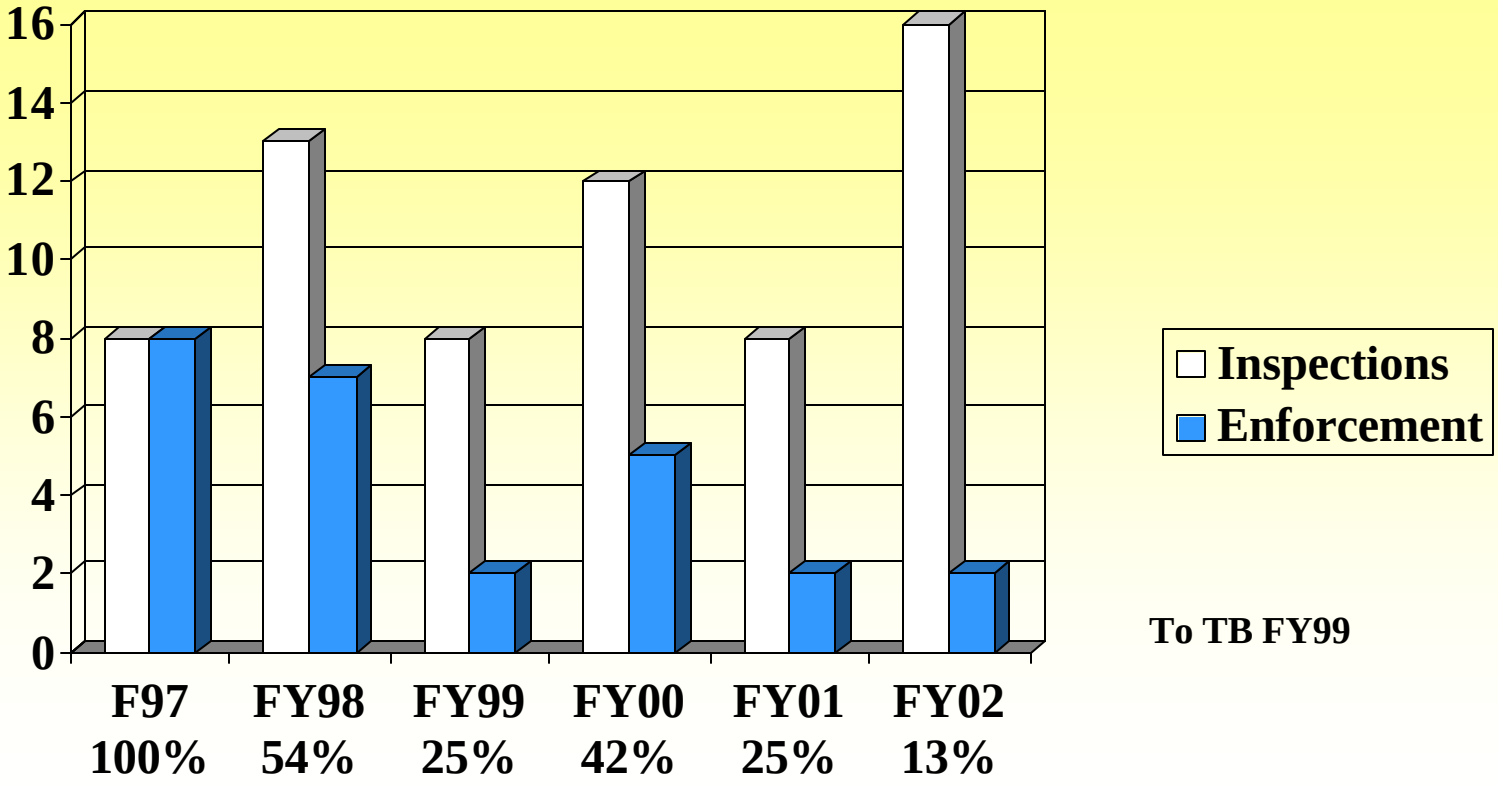


To TB FY 99

Inspections vs. Enforcement Vaccines

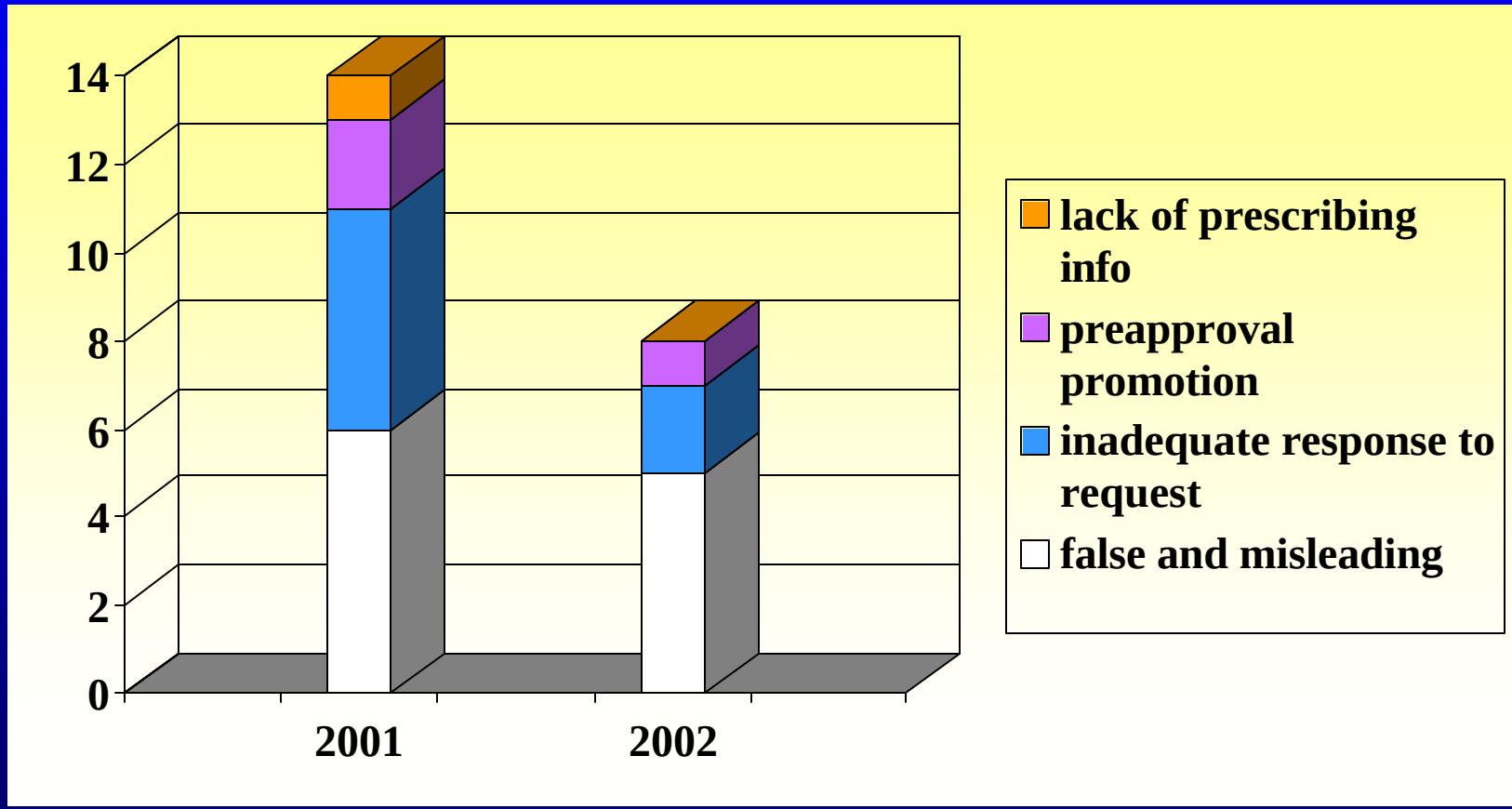


Inspections vs. Enforcement Allergenics

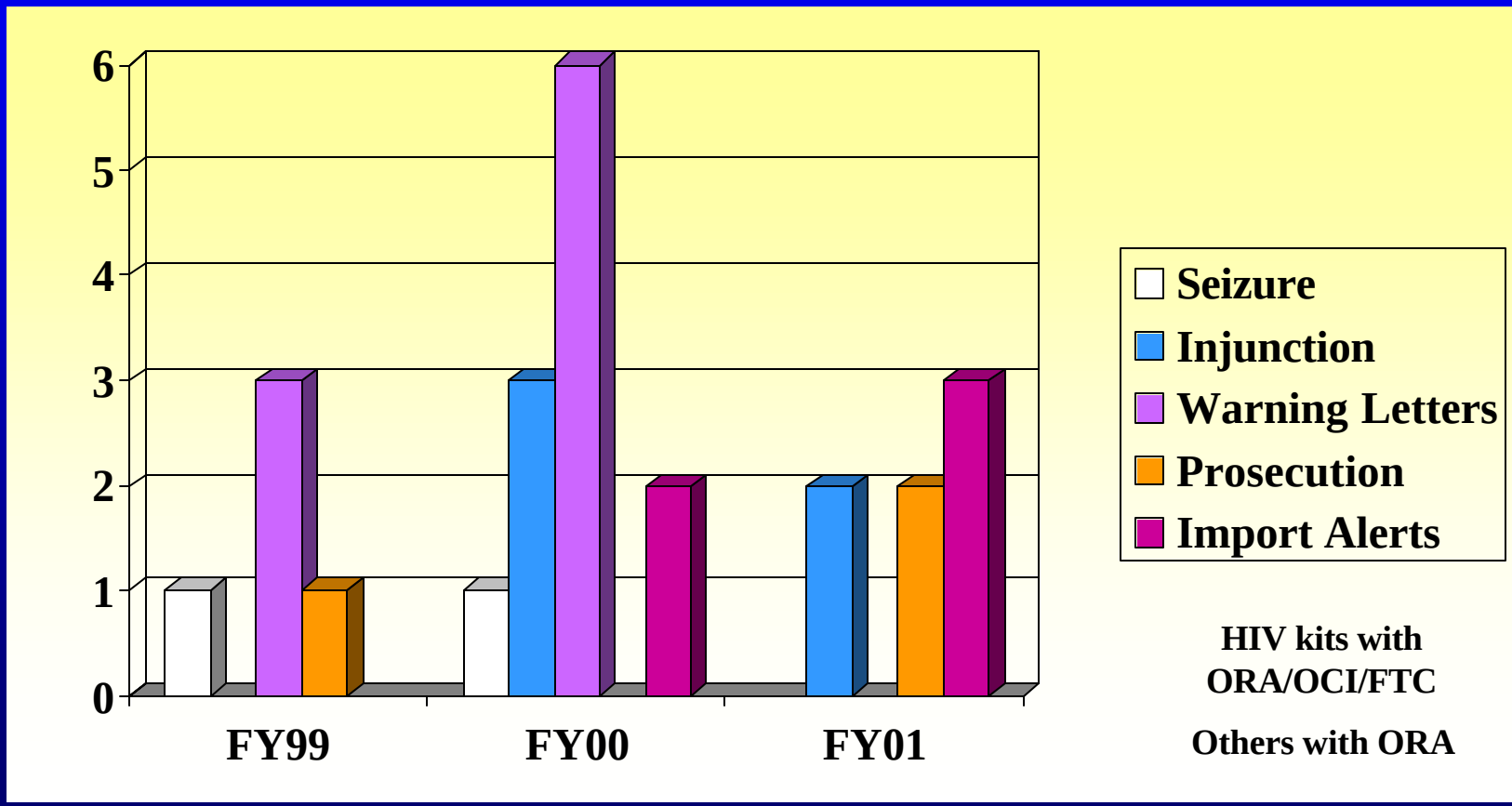


To TB FY99

Promotional Activities



Unapproved Products



Summary

- DCM's responsibilities
  - recalls
  - export/import
  - compliance checks
  - enforcement actions for CBER regulated products
    - CBER initiated
    - CBER concurred

Import/Export Agenda

- **Scope of legislation and how it effects Biological Products**
- **Comparison of new provisions with prior law**

Scope of new law

- Export of unapproved new human drugs and biologics
- Export of approved human drugs and biologics for unapproved indications
- Export of partially processed biological products
- Export of unapproved medical devices
- Import for export
- Certificates for export

Standard Export Requirements

Section 801(e)(1)

- Intended for export
- Accords to the specifications of the foreign purchaser
- Not in conflict with the laws of the country to which it is exported
- Labeled on the outside of the shipping package to show it is intended for export
- Not been offered for sale or sold in domestic commerce

Export of Unapproved New Drugs and Biologics

Prior law

- Limited to list of 21 countries
- Application to FDA required
- Extensive paperwork designed to prevent transshipment
- Sponsor actively seeking approval in U.S.

Export of Unapproved New Drugs and Biologics

Section 802(b)(1)(A)

New provisions

- List of countries from which marketing authorization will allow export **ANYWHERE**
  - Australia
  - Canada
  - Israel
  - Japan
  - New Zealand
  - Switzerland
  - South Africa
  - European Union
  - EEA members

Export of Unapproved New Drugs and Biologics

Section 802(g)

Process

- Simple notification to FDA when begin to export
- Record-keeping
  - Marketing authorization
  - Distribution records
  - Labeling used

Export of Unapproved New Drugs and Biologics

Section 802(f)

Conditions include

- Substantial conformity with GMPs (or FDA-recognized international standards)
- Not otherwise adulterated
- Requirements of 801(e)
- Not an imminent hazard
- Labeled with requirements and conditions for use
  - In the country where it received valid marketing authorization, and
  - In the country to which it is to be exported, and
  - In the language and units of measurement to which it would be exported or language designated by such country
- Promoted as labeled

Export of Unapproved New Drugs and Biologics

Section 802(c)

Investigational products may be exported to a listed country subject only to general conditions of 802(f) and without notification to or approval by FDA

Export of Unapproved New Drugs and Biologics

Section 802(f)

Conditions on investigational use exports include:

- Substantial conformity with GMPs (or FDA-recognized international standards)
- Not otherwise adulterated
- Requirements of 801(e)(1)
- Not an imminent hazard
- Record-Keeping

Export of Unapproved New Drugs and Biologics

Section 802(d)

Export to fill pipeline

- Unapproved products may be exported to a listed country to fill pipeline in anticipation of marketing approval in that country

Section 802(e)

Export for tropical and low prevalence diseases

- Similar to prior law

Export of Partially Processed Biological Products

Section 351(h)

Prior law required FDA approval before partially processed biological products could be exported

New provision allows export without restriction provided product conforms with GMP or international manufacturing standards

AND

Meets the requirements of Section 801(e)(1)

Export of Unapproved Medical Devices

Section 801(e)(2)

Prior law allowed the export of unapproved PMA medical devices if the Secretary of HHS determined that it was not contrary to the public health and safety

Import for Export

Prior law prohibited import of component not in compliance with FFDC Act

Section 801(d)(3)

New provision allows import of component not in compliance if it is to be incorporated into a product that will be exported under 801(e) or 802 of the FFDC Act, or Section 351(h) of the Public Health Service Act (PHS Act)

- **Impact of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002**

Import for Export

Biological Products covered:

- Component of drug
- Component of device

Import for Export

Section 801(d)(4)

Blood, blood components, source plasma, or source leukocytes

- Importation must comply with PHS Act 351(a), or
- Comply with appropriate circumstances and conditions, as determined by FDA

Import for Export

Section 801(d)(4) Import for Export Request (IFER)

For an import for export request to be approved for blood, blood components, source plasma or source leukocytes the following must be met.

- Information on the parties involved, what is being imported, and how it will be incorporated or further processed into a product for export;

Import for Export

Section 801(d)(4) IFER cont.

- The U.S. manufacturer “Should” register and list product for export;
- Description of SOP’s to be implemented to ensure segregation of the imported product/material from U.S. approved products, and to prevent products developed from the imported product from being diverted;

Import for Export

Section 801(d)(4) IFER cont.

- Records of manufacturing, further processing, incorporation, or destruction, and records showing that all the requirements of the appropriate export mechanism have been met; and

- Evidence of an agreement between the U.S. manufacturer and the foreign supplier is strongly suggested.

Import for Export

Section 801(d)(4) IFER cont.

- Labeling of imported material/product. Copies of labeling should be submitted in the import for export request and include the following:
  - Properly descriptive name;
  - Name and address of foreign manufacturer;
  - Donor, Lot, or Pool number;
  - Storage temperature;
  - Quantity;
  - Statement: “Import for Export”;

Import for Export

Section 801(d)(4) IFER cont.

Statement: “For Manufacturing Use Only” for injectable products, or “For Manufacturing into Non-injectable Products Only”;

- Statement: “Not for Use in Products Subject to License under Section 351 of the Public Health Service Act.”;
- Statement that indicates whether or not the product has been tested for all infectious disease agents required and recommended by FDA; and
- Appropriate biohazard labeling.

– Donor Screening questionnaire - Translated into English

– Specifications for the infectious disease testing and expected results

Import for Export

Section 801(d)(4)

Tissue

Importation of tissue or a component or part of tissue is not permitted under this part of the Act, unless it complies with Section 361 of the PHS Act

Export Certificates

- Section 801(e)(4) of FD&C Act
  - Requires FDA to issue requested certificate for human drugs (including biologics) and for devices within 20 days-agency may charge fee if certificate issued within 20 days
  - FDA Compliance Policy Guide Certification for Export (CPG 7150.01) allows for each Center to establish its own internal procedures for an exporter to request certificates.

Types of Export Certificates Issued by CBER

- Certificate to Foreign Government
  - CTT (1270)
- Certificate of Exportability (802)
- Certificate of Exportability (801)
- Certificate of Pharmaceutical Product (WHO Format)
- Non-clinical Research Use Only Certificate

Export Reform

Where are we now?

- FEDERAL REGISTER Draft FDA Guidance for Industry on: Exports and Imports Under the FDA Export Reform and Enhancement Act of 1996 – 02/98, http://www.fda.gov/ohrms/dockets/98fr/061298a.pdf
- FEDERAL REGISTER Import and Export; Reporting and Recordkeeping Requirements for Unapproved or Violative Products Imported for Further Processing or Incorporation and Subsequent Export; Due to BT Act of 2002 the Final Rule has been withdrawn

Export Reform (Cont'd)

Where are we now?

- Federal Register: Exports: Notification and Recordkeeping Requirements; Final Rule – 12/01
  Http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2001_register&docid=01-31026-filed
- Federal Register: Investigational New Drugs: Export Requirements for Unapproved New Drug Products – Proposed Rule 06/02

More Information

- CBER External Web site:
  - www.fda.gov/cber
- Division of Case Management
  - 301-827-6201